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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,577	BOSSY ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-23 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-23 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 15 have been amended. Claims 19-23 have been added. claims 1-23 are pending and under consideration.

Applicant argues against the denial of benefits to the earlier filed application as set forth in the previous office action:

Acknowledgement is made of applicants claim to an earlier effective filing date through dependence on applications 09/619,033, filed 7/19/2000; 60/144, 529, filed 7/19/2000; 10/081,714, filed 2/20/2000; 09/344,308, filed 6/24/1999; and 60/129,384, filed 4/13/1999. Upon review of each of these applications, it is concluded that said applications do not provide support for the instant invention. The instant invention is drawn to a method for identifying "rare events" in a biological sample, which is broader in scope than the methods contemplated in the '033 and '529 applications which were confined to methods of obtaining or enriching a composition with cells having a proliferative disorder. The instant method claims is reliant upon a "rare event" which can encompass such occurrences as detecting a fetal cell in maternal blood, detecting a stem cell in a biological sample comprising sample comprising somatic cells, detecting myocardial cells in peripheral blood, detecting a rare infected cell or rare pathogen in a biological sample. It is concluded that due to the enlargement of the breath of the claims to encompass the detection of cells beyond those cells having a proliferative disorder, that the prior applications fail to provide an adequate description of the claimed invention. Therefore, the instant claims are afforded the priority date of the instant filing date, 7/11/2003.

Applicant maintains that the failure to accord the earliest priority date is in error because the scope of the dependent claims is within the written description of the priority documents which disclosure a method of obtaining and enriching a composition of cells having a proliferative disorder. Applicant emphasizes that the present claims do not have the same scope as that attributed by the examiner to be beyond the disclosure of the priority documents. This has been considered but not found persuasive. Claims 2-22 are ultimately dependent on claim 1. Claim 1 is broader in scope that the subject matter disclosed in the priority documents. It is not

possible to accord a dependent claim a different priority date from the claim on which it depends, because, for art purposes, it would not be possible to reject a dependent claim and not reject the independent claim from whence it depends because 37 CFR states that dependent claims must narrow the scope of independent claims and therefore the subject matter of the dependent claim is encompassed by the independent claim.

Applicant argues that the disclosure of detection of proliferative cells in the priority document would satisfy the written description requirement of 112, first paragraph, because this constitutes a "representative number" and one of skill in the art would recognize that applicant was in possession of the claimed genus of rare events. This has been considered but not found persuasive. The examiner maintains that the disclosure of isolating/identifying cells associated with a proliferative disorder does not adequately describe a method of isolating/identifying cells associated with a rare event, such as a fetal cell in the maternal blood, a myocardial cell resulting from cardiac injury, an infected cell or a pathogen, such as a free parasite. One of skill in the art would not have concluded that applicant was in possession of these alternate embodiments after reading the priority documents disclosing a proliferative disorder, because there was no disclosure that would suggest that fetal cells or myocardial cells or cells of a pathogen, such as a parasite, or cells resulting from other disorders, such as intestinal disorders, would be found circulating in blood or a particular body fluid as a result of a pathological condition. There was no disclosure as to the reagents necessary for the detection of an infected cell. Thus, the description of isolation/detection of cells associated with proliferative disorder does not adequately describe the instant genus encompassing isolation/detection of cells associated with a rare event.

Applicant is invited to amend claim 1 to reflect the scope of the disclosures f the priority documents

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear how the final method step of claim 20 "obtaining additional images of the candidate rare event" pertains to the method objective of claim 20, requiring "processing the plurality of images" because "obtaining" a piece of data is not commensurate with the "processing" of said piece of data.

Claim 20 recites "having a filed of view larger than the fields of views of the plurality of images. the metes and bound of this statement cannot be construed because the composition image can only provide a filed of view which is the sum of its part, which would provide a filed of view larger than the field of view of an individual image, not of the plurality of images.

It is unclear how the active method step of claim 23 further limits the scope of claim 22 because "presenting the mosaic to a user" is not commensurate with the processing of images. further, claim 23 is vague and indefinite because it is unclear who is intended to be within the metes and bounds of a "user", which can encompass scientists, medical doctors, and clerical staff which enter data into a database.

The rejection of claims 1-4, 6-13, 17 and 18 under 35 U.S.C. 102(e) and 35 U.S.C. 102(a) as being anticipated by O'Hara et al (WO 03/035895) is maintained for reasons of record.

Claim 1 is drawn to a method for identifying rare events in a biological sample, comprising: obtaining a source of cells; contacting the source with a binding agent specific for a cell specific marker associated with a rare event wherein the binding agent is bound to a magnetic bead and wherein the binding agent binds to cells in the source expressing the cell specific marker; separating cells bound by the binding agent from the source thereby obtaining a sub-population of cells enriched for the cell specific marker associated with the rare event; placing the enriched sample on a substrate; automatically scanning the substrate at a plurality of coordinates; automatically obtaining a plurality of images at locations on the substrate that comprise the enriched sample; and processing the plurality of image to identify the rare event. Claim 2 embodies the method of claim 1, wherein the binding agent is an antibody. Claim 3 embodies the method of claim 1, wherein the sub-population is enriched for carcinoma cells.

Claim 4 embodies the method of claim 1, wherein the separating is done by positive selection. Claim 6 embodies the method of claim 2, wherein the antibody is monoclonal or polyclonal. Claim 7 embodies the method of claim 2, wherein the antibody recognizes an epithelial marker. Claim 8 embodies the method of claim 2, wherein the antibody is selected to avoid cross reactivity with the beads. Claim 9 embodies the method of claim 3, wherein the carcinoma cells are from peripheral blood. Claim 10 embodies the method of claim 1, further comprising: (a) automatically identifying a coordinate of the rare event; and (b) automatically acquiring an image of the rare event, at the location coordinates. Claim 11 embodies the method of claim 1, wherein the rare event is detected by immunohistochemistry. Claim 12 embodies the method of method of claim 1, wherein the rare event is detected by in situ hybridization. Claim 13 embodies the method of claim 1, wherein the rare event is detected by a stain. Claim 17 embodies the method of claim 1, wherein the cell specific marker is detected by immunohistochemistry, in situ hybridization, staining or a combination thereof. Claim 18 embodies the method of claim 1, wherein the image is a digital image.

O'Hara et al disclose a method of diagnosing the presence and the severity of a disease comprising detecting the presence of circulating cancer cells (page 15, second full paragraph and page 16, first paragraph). O'Hara et al disclose that cancers cells of epithelial origin can be isolated from patient blood or bone marrow sample by using immunomagnetic particle which bind to cancer cells (page 5, lines 5-7). O'Hara et al teach that the immunomagnetic particles comprise an EPCAM ferrofluid which comprise a monoclonal antibody which reacts with EpCAM on epithelial cells (page 40, lines 1-4), thus fulfilling the specific embodiment of an antibody which fulfills the specific embodiments of claims 6 and 7 . O'Hara et al disclose in situ hybridization combined with immunohistochemistry for the detection of circulating cancer cells (page 28, lines 17-21, page 17, lines 21-25 and page 20, third paragraph), which fulfills the specific embodiments of claim 11, 12, 13 and 15. O'Hara et al disclose the detection of mRNA can proceed with automation (page 28, lines 6-10), thus fulfilling the specific embodiment of claim 10. O'Hara et al disclose multiparameter flow cytometry, and image analysis (page 1 under "Field of the Invention") which fulfills the specific ;limitations of claim 18 requiring a digital image. Further, it would have been inherent in the method of O'Hara et al that the anti-EpCAM antibody was selected to avoid cross-reactivity with the beads in order that the

antibody-binding valency is preserved for reactivity with the target antigen on the cancer cells (page 18, third full paragraph).

The rejection of claims 1-4, 6-14, 16, 17 and 18 under 35 U.S.C. 102(e) and 35 U.S.C. 102(a) as being anticipated by Pachmann et al (US 2003/0017514) is maintained for reasons of record.

Claim 14 embodies the method of claim 13 wherein the stain is a nucleic acid dye selected from a group including propidium iodide. Claim 16 embodies the method of claim 1 wherein the cell specific marker is detected by a nuclear stain and a counter stain.

Pachmann et al disclose a method for detecting and isolating vital tumor cells in body fluids, in particular peripheral blood (paragraph 0017) comprising using anti epithelial antibodies bound to magnetic particles, wherein the tumor cells are additionally labeled by an anti-epithelial antibody bound to a fluorochrome (claims 1-10). Pachmann et al disclose that the isolated tumor cells can be placed on a solid support and scanned by a laser(paragraph 0023). Packman et al further disclose that further detection methods can be carried out on the cells because each cell can be immediately located and it reaction to other detection substances can be recorded (paragraph 0027) which fulfills the specific limitation of claim 10 requiring the identification of a rare event at a "coordinate". Packman et al disclose that said cells can be further labeled with propidium iodide stain (paragraph 0024) thus fulfilling the specific embodiment of claims 14 and 16 because the combination of propidium iodide with another stain is equivalent to a nuclear stain and a counter stain. Packman et al disclose that morphology of the recorded positive cells can then be determined by hematological staining methods (paragraph 0026) which fulfills the specific embodiments of immunohistochemcial staining in claim 13. Packman et al disclose that FISH can be carried out on the isolated cells along with other detection methods (paragraph 0027) which fulfills the specific embodiments of claim 17 because FISH incorporated in situ hybridization. it would have been inherent in the method of Packman et al that the anti-epithelial antibody was selected to avoid cross-reactivity with the beads in order that the antibody-binding valency is preserved for reactivity with the target antigen on the cancer cells.

The rejection of claims 1-4, 6-13, 17 and 18 under 35 U.S.C. 102(b) as being anticipated by Liberti et al (WO 02/06790) is maintained for reasons of record.

Liberti et al disclose a method of detecting and isolating tumor cells, virally infected cells, fetal cells in maternal circulation, virus particles, bacterial cells, white blood cells, myocardial cells, epithelial cells, and endothelial cells in body fluids (claims 1, 3 and 6),. Liberti et al disclose that cancers cells of epithelial origin can be isolated from patient blood or bone marrow sample by using immunomagnetic particle which bind to cancer cells (claims 2 and 4). Liberti et al teach that the immunomagnetic particles comprise a monoclonal or polyclonal anti-epithelial antibody attached to supermagnetic particles (claim 11), thus fulfilling the specific embodiment of an antibody which fulfills the specific embodiments of claims 6 and 7 . Liberti et al disclose the staining of the isolated cells for intracellular antigens (page 49, lines 10-15) which fulfills the specific embodiment of immunohistochemistry which fulfills the specific embodiments of claim 11, 13 and 17. Liberti et al disclose multiparameter flow cytometry, and image analysis (claim 7) which fulfills the specific limitations of claim 10 and 18 requiring a digital image and the association of a rare event with a particular coordinate. Further, it would have been inherent in the method of Liberti et al that the anti-epithelial antibody was selected to avoid cross-reactivity with the beads in order that the antibody-binding valency is preserved for reactivity with the target antigen on the cancer cells. .

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-4, 6-14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hara et al (WO 03/035895) in view of Grizwald et al (Journal of Immunochemical Methods, 1995, Vol. 183, pp.251-265) is maintained for reasons of record..

O'Hara et al teach the specific limitations of claims 1-4, 6-13, 17 and 18 for the reasons set forth above. O'Hara et al do not specifically teach propidium iodide staining and a counter stain.

Grizwald et al teach the combination of propidium iodide staining as a counter stain to staining with an anti human PSA antibody (page 255 under section 2.12).

It would have been prima facie obvious at the time the claimed invention was made to combining the histological stating of the isolated cancer cells with propidium iodide counter stain. One of skill in the art would have been motivated to do so in order to provide more morphological data regarding the isolated cell population. Because propidium iodide only stains double stranded DNA said stain will provide the nuclear reference point for any other non-nuclear staining in the cell cytoplasm or membrane. One of skill in the art would understand that the nuclear staining with propidium iodide would provide a reference point for further qualification of reactivity with other stains.

The rejection of claims 1-4, 6-14 and 16-18 under 35 U.S.C. 103(a) as being unpatentable over Liberti et al (WO 02/06790) in view of Grizwald et al (Journal of Immunochemical Methods, 1995, Vol. 183, pp.251-265) is maintained for reasons of record. .

Liberti et al teach the specific limitations of claims 1-4, 6-13, 17 and 18 for the reasons set forth above. Liberti et al do not specifically teach propidium iodide staining and a counter stain.

Grizwald et al teach the combination of propidium iodide staining as a counter stain to staining with an anti human PSA antibody (page 255 under section 2.12).

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nuclear staining in the cell cytoplasm or membrane. One of skill in the art would understand that the nuclear staining with propidium iodide would provide a reference point for further qualification of reactivity with other stains.

The rejection of claims 1-4, 6-14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hara et al (WO 03/035895) and Grizwald et al (Journal of Immunochemical Methods, 1995, Vol. 183, pp.251-265).as applied to claims 1-14 and 16-18 above, and further in view of Singer et al (U.S. 6,323,337) is maintained for reasons of record..

Claim 14 further includes the stains of YOYO, TOTO and SYTOX. Neither O'Hara et al nor Grizwald et al teach said stains.

Singer et al teach the nucleic acid stains of YOYO, TOTO and SYTOX exhibit enhanced fluorescence when associated with nucleic acids (column 14, lines 28-46).

It would have been prima facie obvious at the time the claimed invention was made to substitute YOYO, TOTO and SYTOX for propidium iodide in the method rendered obvious by the combination of O'Hara et al and Grizwald et al. One of skill in the art would have been motivated to do so by the teachings of Singer et al on the improvement afforded by the use of nucleic acid dyes YOYO, TOTO or SYTOX.

The rejection of claims 1-4, 6-14 and 16-18 under 35 U.S.C. 103(a) as being unpatentable over Pachmann et al (US 2003/0017514) in view of Singer et al (U.S. 6,323,337) is maintained for reasons of record.

Claim 14 further includes the stains of YOYO, TOTO and SYTOX. Packman et al does not teach said nucleic acid stains.

Singer et al teach the nucleic acid stains of YOYO, TOTO and SYTOX exhibit enhanced fluorescence when associated with nucleic acids (column 14, lines 28-46).

It would have been prima facie obvious at the time the claimed invention was made to substitute YOYO, TOTO and SYTOX for propidium iodide in the method of Packman et al. One of skill in the art would have been motivated to do so by the teachings of Singer et al on the improvement afforded by the use of nucleic acid dyes YOYO, TOTO or SYTOX.

The rejection of claims 1-4, 6-14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liberti et al (WO 02/06790) and Grizwald et al (Journal of Immunochemical Methods, 1995, Vol. 183, pp.251-265).as applied to claims 1-14 and 16-18 above, and further in view of Singer et al (U.S. 6,323,337) is maintained for reasons of record..

Claim 14 further includes the stains of YOYO, TOTO and SYTOX. Neither Liberti et al nor Grizwald et al teach said stains.

Singer et al teach the nucleic acid stains of YOYO, TOTO and SYTOX exhibit enhanced fluorescence when associated with nucleic acids (column 14, lines 28-46).

It would have been prima facie obvious at the time the claimed invention was made to substitute YOYO, TOTO and SYTOX for propidium iodide in the method rendered obvious by the combination of Liberti et al and Grizwald et al. One of skill in the art would have been motivated to do so by the teachings of Singer et al on the improvement afforded by the use of nucleic acid dyes YOYO, TOTO or SYTOX.

The rejection of claims 1-4, 6-15 and 17-18 under 35 U.S.C. 103(a) as being unpatentable over O'Hara et al (WO 03/035895) in view of Bloom and Fawcett (A Textbook of Histology, 1962, page 15) is maintained for reasons of record. Claim 14 embodies the method of claim 13 wherein the dye is selected from a group including hematoxylin. Claim 15 embodies the method of claim 13 wherein the dye is eosin.

O'Hara et al do not specifically teach the dyes of hematoxylin and eosin.

Bloom and Fawcett teach that hematoxylin and eosin is the most common histological staining method.

It would have been prima facie obvious at the time the claimed invention was made, to include the dyes hematoxylin and eosin in the method of O'Hara et al. One of skill in the art would have been motivated to do so by the teachings of Bloom and Fawcett regarding the common use of hematoxylin and eosin. One of skill in the art would know that the use of this combination would enable comparisons with other tumor cells stained by the same combination.

The rejection of claims 1-4, 6-15 and 17-18 under 35 U.S.C. 103(a) as being unpatentable over Pachmann et al (US 2003/0017514) in view of Bloom and Fawcett (A Textbook of Histology, 1962, page 15) is maintained for reasons of record..

Packman et al do not specifically teach the dyes of hematoxylin and eosin. Bloom and Fawcett teach that hematoxylin and eosin is the most common histological staining method. It would have been prima facie obvious at the time the claimed invention was made, to include the dyes hematoxylin and eosin in the method of Packman et al. One of skill in the art would have been motivated to do so by the teachings of Bloom and Fawcett regarding the common use of hematoxylin and eosin. One of skill in the art would know that the use of this combination would enable comparisons with other tumor cells stained by the same combination.

The rejection of claims 1-4, 6-15 and 17-18 under 35 U.S.C. 103(a) as being unpatentable over Liberti et al (WO 02/06790) in view of Bloom and Fawcett (A Textbook of Histology, 1962, page 15) is maintained for reasons of record.

Liberti et al do not specifically teach the dyes of hematoxylin and eosin. Bloom and Fawcett teach that hematoxylin and eosin is the most common histological staining method. It would have been prima facie obvious at the time the claimed invention was made, to include the dyes hematoxylin and eosin in the method of Liberti et al. One of skill in the art would have been motivated to do so by the teachings of Bloom and Fawcett regarding the common use of hematoxylin and eosin. One of skill in the art would know that the use of this combination would enable comparisons with other tumor cells stained by the same combination.

The rejection of claims 1-13, 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over O'Hara et al (WO 03/035895) in view of Thomas et al (U.S. 6,117,985) is maintained for reasons of record.

Claim 5 embodies the method of claim 1 wherein the separating is done by negative selection.

O'Hara et al teach the separating by positive selection. O'Hara et al do not teach separating by negative selection.

Thomas el al teach separating non-hematopoietic tumor cells from a sample comprising hematopoietic cells (claims 1-11).

It would have been prima facie obvious to use the negative selection method of Thomas et al prior to the positive selection method of O'Hara et al. One of skill in the art would have been motivated to combine the two methods because they are both recognized in the art as method for the isolation of rare tumor cells and it would be expected that both methods would contribute to the isolation of a population of tumor cells.

The rejection of claims 1-14, 16, 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Pachmann et al (US 2003/0017514) in view of Thomas et al (U.S. 6,117,985) is maintained for reasons of record.

Packman et al teach separating by positive selection rather than by negative selection.

Thomas el al teach separating non-hematopoietic tumor cells from a sample comprising hematopoietic cells (claims 1-11).

It would have been prima facie obvious to use the negative selection method of Thomas et al prior to the positive selection method of Packman et al. One of skill in the art would have been motivated to combine the two methods because they are both recognized in the art as method for the isolation of rare tumor cells and it would be expected that both methods would contribute to the isolation of a population of tumor cells.

The rejection of claims 1-13, 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Liberti et al (WO 02/06790) in view of Thomas et al (U.S. 6,117,985) is maintained for reasons of record.

Liberti et al teach separating by positive selection rather than by negative selection.

Thomas el al teach separating non-hematopoietic tumor cells from a sample comprising hematopoietic cells (claims 1-11).

It would have been prima facie obvious to use the negative selection method of Thomas et al prior to the positive selection method of Liberti et al et al. One of skill in the art would have been motivated to combine the two methods because they are both recognized in the art as

method for the isolation of rare tumor cells and it would be expected that both methods would contribute to the isolation of a population of tumor cells.

Claims 1-4, 6-14, 16-18 and 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pachmann et al (US 2003/0017514) in view of McLaren et al (U.S. 6,546,123).

Claim 20 embodies the method of claim 1 wherein processing the plurality of images comprises placing adjacent of the images together to generate a composite image having a file of view larger than the fields of view of the plurality of images. Claim 21 embodies the method of claim 1 wherein processing the plurality of images comprises identifying a candidate rare event, determining coordinates for said rare event and obtaining additional images of the candidate rare event. Claim 22 embodies the method of claim 1 wherein processing the plurality of images comprises identifying a collection of candidate rare events and generating a mosaic comprising images of the candidate rare event in the collection. Claim 23 embodies the method of claim 22 wherein the plurality of images further comprises presenting the mosaic to the user.

Pachmann et al teach a method for detecting and isolating vital tumor cells in body fluids, in particular peripheral blood (paragraph 0017) comprising using anti epithelial antibodies bound to magnetic particles, wherein the tumor cells are additionally labeled by an anti-epithelial antibody bound to a fluorochrome (claims 1-10). Pachmann et al teach that the isolated tumor cells can be placed on a solid support and scanned by a laser(paragraph 0023). Packman et al further teach that further detection methods can be carried out on the cells because each cell can be immediately located and it reaction to other detection substances can be recorded (paragraph 0027) which fulfills the specific limitation of claim 10 requiring the identification of a rare event at a "coordinate". Packman et al teach that said cells can be further labeled with propidium iodide stain (paragraph 0024) thus fulfilling the specific embodiment of claims 14 and 16 because the combination of propidium iodide with another stain is equivalent to a nuclear stain and a counter stain. Packman et al teach that morphology of the recorded positive cells can then be determined by hematological staining methods (paragraph 0026) which fulfills the specific embodiments of immunohistochemcial staining in claim 13. Packman et al teach that FISH can be carried out on the isolated cells along with other detection methods (paragraph 0027) which

fulfills the specific embodiments of claim 17 because FISH incorporated in situ hybridization. it would have been inherent in the method of Packman et al that the anti-epithelial antibody was selected to avoid cross-reactivity with the beads in order that the antibody-binding valency is preserved for reactivity with the target antigen on the cancer cells. Packman et al do not specifically teach generating a composite of candidate rare events or presenting them to the user.

McLaren et al teach a method of imaging rare events such as a tumor cell, comprising storing images as mosaics (column 19, lines 21-37). McLaren et al teach that the mosaic of saved images can be made available for viewing to the pathologist (column 27, lines 1-8) which fulfills the specific limitation of claim 23 regarding the "user"..

It would have been prima facie obvious at the time the claimed invention was made to use the method of processing images of rare events as taught by McLauren in the method of identifying tumor cells as rare events a taught by Pachmann One of skill in the art would have been motivated to provide such a composite image in order to maximize the number of tumor cells which can be visualized in binding to a probe in an assay for labeling. One of skill in the art would be motivated to transmit such data to "the user" who can then provide diagnostic information to the patient.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn in light of applicants amendments.

All claims are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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